1: Genet Test 1997;1(1):13-9

Niemann-Pick disease: mutation update, genotype/phenotype correlations, and prospects for genetic testing.

Schuchman EH, Miranda SR.

Department of Human Genetics, Mount Sinai School of Medicine, New York, NY 10029, USA.

Niemann-Pick Disease (NPD) is an autosomal recessive lysosomal storage disorder caused by a deficiency of acid sphingomyelinase (ASM). NPD occurs in two forms, neuronopathic Type A and nonneuronopathic Type B. The incidence of Type A NPD is highest among Ashkenazi Jews. Type B NPD is more common in non-Jews but has been reported in Ashkenazi Jews. Different mutations in ASM are presumed to be responsible for the different NPD phenotypes. Three mutations are predicted to account for > 95% of all Type A NPD chromosomes among Ashkenazi Jews (L302P, R496L, fsP330). Based on limited screens for these mutations among Ashkenazi Jews, a carrier frequency for Type A NPD of 1:90 is reported for this population. Less is known about mutations responsible for Type B NPD, although one mutation (delta R608) has been identified in both Ashkenazi Jews and non-Jews. Screening of the Ashkenazi Jewish population to detect > 95% of NPD carriers can be accomplished with a four-mutation panel that includes L302P, R496L, fsP330, and delta R608, the three predominant Type A mutations and one recurrent Type B mutation.

Publication Types:
- Review
- Review, Tutorial

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Gaucher disease: gene frequencies and genotype/phenotype correlations.

Grabowski GA.

Children's Hospital Research Foundation, Cincinnati, OH 45229-3039, USA.

Gaucher disease is the most prevalent lysosomal storage disease and has its highest incidence in the Ashkenazi Jewish population. Over 100 mutant alleles have been identified in affected patients, but four alleles, termed N370S, L444P, 84GG, and IVS2, have significant frequencies in this population. In affected patients, genotype data show that the presence of a single N370S allele is diagnostic of the type 1 or nonneuronopathic variant, whereas the L444P/L444P genotype is highly associated with neuronopathic variants in the Caucasian population. Large screening studies also indicate a significant underestimation (approximately two-fold) of the prevalence of the N370S/N370S genotype in the affected Ashkenazi Jewish patient population. These results indicate that the N370S/N370S genotype provides a necessary but not sufficient condition for the development of the Gaucher disease phenotype. The genotype/phenotype correlations and gene frequencies have significant impact on genetic counseling of at-risk couples and the future need for therapy of affected patients.

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